NEUROLOGY Therapy

Headache

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Headache-prone patients have many highly effective therapeutic options open to them. Used only at the time of headache, sumatriptan succinate by mouth or injection and dihydroergotamine nasal spray are novel choices now or soon to be available. The original migraine therapy, ergotamine, is highly effective in its rectal suppository formulation, when used at a subnauseating dosage. Valproate sodium is the latest addition to the many therapies available for long-term stabilization.

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Most of us are subject to headache from time to time. The mechanism for generating ordinary headaches may be activated by worry and anxiety, but stress does not appear to be necessary for the symptom to occur.[1,2] Genetic factors may augment this system, resulting in a susceptibility to more frequent or more severe head pain, with or without associated neurologic symptoms.[3] The term "migraine" is being used increasingly to refer to such a susceptibility to head pain in contradistinction to its previous usage as an aggregation of certain symptoms. Thus, stress-related headaches, perhaps the commonest syndrome reported by patients, are examples of the expression of this susceptibility after provocation by an adequate stimulus; a similar, if not identical, mechanism is identified by the activation of headache by red wine, normal menses, and exposure to glare and certain odors.[4]

The drugs that have proved to be effective in treating migraine were uncovered empirically or for actions later shown to be unrelated to the benefits observed clinically. These agents traditionally have been classified according to their actions in other conditions for which an effect outside the central nervous system has usually been implicated. Included in this group are vasoconstrictors (ergotamine tartrate, dihydroergotamine mesylate, sumatriptan succinate), serotonin antagonists (methysergide maleate, cyproheptadine hydrochloride), β-adrenergic receptor blockers (propranolol hydrochloride, nadolol), an antidepressant (amitriptyline hydrochloride), and antiprostaglandins (naproxen, ketoprofen) (Figure 1). There is evidence that the effect of propranolol in migraine is mediated by an action other than, or in addition to, β-adrenergic receptor blockade and, similarly, that amitriptyline probably does not act as an antidepressant. Although it is possible that some of these actions are relevant to the drugs' effectiveness in migraine, several lines of evidence suggest that their common mode of action may be to stabilize central inhibitory mechanisms.[5]

The introduction of sumatriptan, a selective agonist of a specific subgroup of serotonin receptors and an unusually effective agent in aborting acute headache attacks, has awakened interest in the treatment of this common ailment. In this review I focus on therapeutic advances in this area.

Treatment of Acute Headache or Migraine

In general, an adequate dose of whichever agent is chosen should be used at the start of an attack. If additional medication is required in 30 to 60 minutes because symptoms return or have not abated, the initial dosage should be increased for subsequent attacks. Drug absorption is impaired during attacks because of reduced gastrointestinal motility. Absorption is delayed in the absence of nausea and is related to the severity of the attack but not the duration.[6] Therefore, when oral agents fail, the major options are rectal administration of ergotamine, subcutaneous sumatriptan, parenteral dihydroergotamine, and intravenous chlorpromazine hydrochloride or prochlorperazine maleate.

For patients with a prolonged buildup of headache, oral agents may suffice. When aspirin and acetaminophen fail, the addition of butalbital and caffeine to these analgesics is highly effective; ibuprofen (600 to 800 mg) and naproxen (375 to 750 mg) are often useful. Isometheptene compound,* one to two capsules, is effective for mild to moderate "stress headaches."[7] When these measures fail, more aggressive therapy should be considered.

Ergotamine Tartrate

The oral and rectal absorption of ergotamine tartrate is unpredictable, as it varies widely among individual patients. Bioavailability is less than 5% for the oral dosage form, but it is considerably higher after rectal dosing.[8] Peak plasma concentrations are reached about an hour after oral or rectal dosing. Plasma levels after rectal admin-

*All isometheptene compounds contain 65 mg of isometheptene mucate, 100 mg of dichloralphenazone, and 325 mg of acetaminophen.

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ABBREVIATIONS USED IN TEXT

DHE = dihydroergotamine
NSAIDs = nonsteroidal anti-inflammatory drugs

istration are higher; one study showed levels 20 times higher.[9] Effectiveness, as assessed by peripheral arterial constriction, is much greater after rectal than oral administration of the drug. Its biologic effects last much longer than its short elimination half-life of two to three hours would suggest.

Ergotamine produces powerful and selective constriction of the external carotid artery and its branches. Only slight α-adrenergic blockade occurs at doses used clinically, and the vasoconstrictor effect is mediated by a direct effect on arterial serotonin receptors. Extracranial arterial constriction is likely important to ergotamine's efficacy, but the extracranial arteries may not be the drug's primary site of action. Several ergot alkaloids have been found to depress the firing rate of serotonergic neurons of the brain-stem raphe, the origin of inhibitory projections to the forebrain; thus, stabilization of this system may be the major mode of action of ergotamine.[5]

An adequate dose should be taken as soon as possible—not divided into half-hourly or hourly supplements; if the initial dose fails, subsequent doses usually fail also. If possible, a dose that does not cause nausea should be determined. A dose that provokes nausea—probably a centrally mediated side effect—is too high and may even intensify a migraine attack. The appropriate dosage of ergotamine is best arrived at by determining the patient's capacity to tolerate ergotamine during a headache-free period. The average dose of a rectal suppository is half (1 mg), so that if a patient is seen for the first time during a headache attack, I give 1 mg immediately, and if there is no evidence of improvement in 45 minutes, another 1-mg dose may be given.

Dihydroergotamine Mesylate

Introduced about ten years after ergotamine, dihydroergotamine mesylate (DHE) was found to be at least equally effective in aborting acute attacks of migraine. In contrast to ergotamine, DHE produces only modest arterial constriction[10] but is a potent venoconstrictor.[11] As with ergotamine, idiosyncratic hypersensitivity to the drug occasionally occurs, and rare instances of severe peripheral arterial spasm and coronary spasm have been reported.[12] Unlike ergotamine, DHE does not produce physical dependence.[13]

Given intravenously, DHE produces less nausea than ergotamine, and thus, if preceded by an antiemetic, it can be used when a migraine attack is attended by vomiting.[14,15] Subcutaneous or intramuscular administration of 1 mg usually suffices for 90% of patients.[16] Patients can be taught to administer a subcutaneous dose. A nasal instillation form is not as effective.

Adverse effects of the drug may include diarrhea, leg muscle pain, and abdominal discomfort. Patients with Prinzmetal's angina should be excluded from this therapy

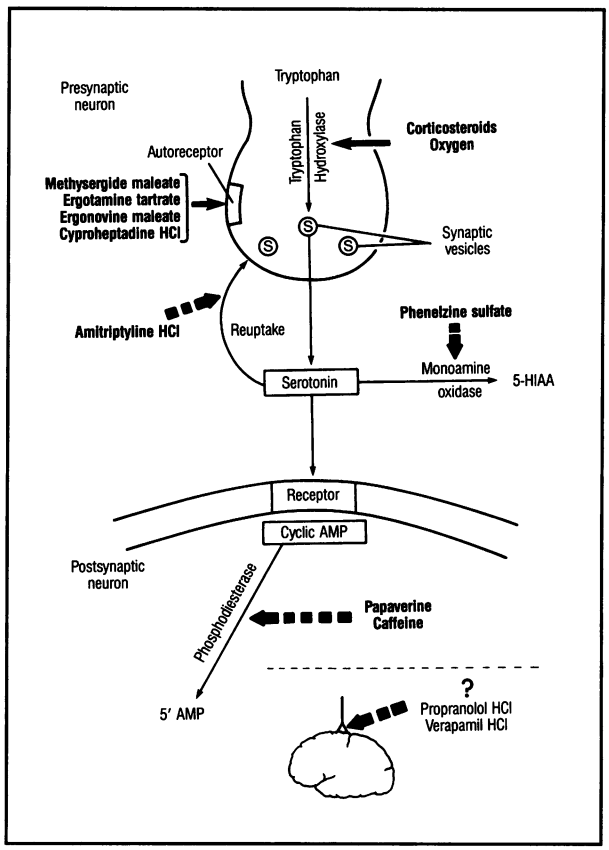

Figure 1.—The diagram shows the actions of the antimigraine drugs at the brain-stem and forebrain synapses. The **solid arrows** indicate stimulative or agonist properties; the **segmented arrows** indicate inhibitory properties. 5′ AMP = 5′-adenosine monophosphate, cyclic AMP = adenosine 3′:5′-cyclic phosphate, HCl = hydrochloride, 5-HIAA = 5-hydroxyindoleacetic acid

because of the risk of precipitating attacks through ergot hypersensitivity. Like other ergot derivatives, DHE is contraindicated in pregnancy.

The venoconstrictor effect of DHE persists for about eight hours after intravenous administration.[11] The major metabolite of DHE, 8′-hydroxy-dihydroergotamine, reaches plasma concentrations that are five to seven times higher than those of DHE itself and possesses similar pharmacologic effects.[17] Pharmacodynamic efficacy persists after drug withdrawal and in the absence of measurable drug levels.[11] Both DHE and its major metabolite bind selectively to brain serotonin receptors. Dihydroergotamine's lack of important arterial constrictor effects emphasizes the importance of these central receptor actions to the agent's action in migraine.

Phenothiazines

Two controlled studies have clearly demonstrated that intravenous chlorpromazine hydrochloride, 0.1 mg per kg of body weight,[18] and prochlorperazine maleate, 10 mg,[19] are highly effective in terminating migrainous episodes. The chlorpromazine protocol allowed for repeating the dose every 15 minutes as needed for a total of three doses; of the 24 patients who received chlorpromazine, 6 re-

TABLE 1.—*Drug Stabilization of Migraine*

Drug	Tablet Size, mg	Daily Dose Range, mg	Most Common Side Effects
Propranolol hydrochloride.....	10, 20, 40, 60, 80, 90 Sustained-release: 60, 80, 120, 160	40-320	Fatigue, insomnia, lightheadedness, impotence
Amitriptyline hydrochloride.....	10, 25, 50, 75, 100	10-175	Sedation, dry mouth, appetite stimulation
Ergonovine maleate.....	0.2	0.4-2.0	Nausea, abdominal pain, leg tiredness, diarrhea
Verapamil hydrochloride.....	40, 80, 120 Sustained-release: 120, 180, 240	160-480 320-960	Constipation, nausea, fluid retention, lightheadedness, hypotension
Valproate sodium.....	125, 250, 500	375-2,500	Nausea, tremor, alopecia, appetite stimulation
Phenelzine sulfate.....	15	30-90	Sedation, orthostatic hypotension, constipation, urinary retention
Methysergide maleate.....	2	2-12	Nausea, abdominal pain, insomnia, appetite stimulation, fluid retention, limb claudication

quired only one dose, 9 received two doses, and another 9 had three doses. Because phenothiazines confer no physical dependence, these results have important practical implications. Prochlorperazine and DHE are miscible, so that both drugs may be administered simultaneously with a single venipuncture.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have become important for the treatment of migraine,[20,21] in part because they do not generate a cycle of dependency. The NSAIDs are analgesic when tested in acute pain models, and this property can be shown to be independent of prostaglandin synthesis inhibition,[22,23] which is the common pharmacologic action of drugs in this class. Evidence is emerging that the central actions of NSAIDs best explain their analgesic properties. The analgesic actions of acetylsalicylic acid and acetaminophen may also be centrally mediated.[24-26]

Among the NSAIDs, naproxen is favored for migraine treatment because of its efficacy, tolerance, and safety record. It is completely absorbed after oral or rectal administration, with peak plasma concentrations reached an hour after naproxen sodium administration and two hours after naproxen administration.[27] The more rapid absorption of the sodium salt enhances efficacy for the management of acute headache episodes. The biologic half-life of naproxen is 12 to 15 hours. Plasma levels increase linearly with doses as high as 750 mg; at higher doses they continue to rise, although at a lesser rate. Thus, for an acute attack, a dose of no less than 750 mg should be considered.

Initial enthusiasm for this group of drugs for daily use must now be tempered because of the enteropathy that occurs with long-term use. When used for six months or longer, subclinical intestinal inflammation and occult blood loss develop in more than two thirds of patients.[28] As many as a fifth of them have bile acid malabsorption, and thus diarrheal illnesses may develop. Fewer than 1% have ulceration and strictures. In view of this experience and because there are so many alternatives for prophylaxis, the NSAIDs should not be used long term and daily in migraine therapy.

Sumatriptan Succinate

Sumatriptan was developed as an agonist specific to serotonin receptors, which occur not only in the midbrain dorsal raphe but also in the extracranial vasculature. Unique among antimigraine drugs, sumatriptan is devoid of activity in receptor systems other than serotonin receptors, probably accounting for its mild side-effect profile. The selective action of sumatriptan provides an important clue to the effective mode of action of other antimigraine drugs that have multiple sites of activity because sumatriptan binds only to serotonin receptors and effectively terminates migraine symptoms.[29]

Sumatriptan is distinctive in being the most extensively studied antimigraine agent in history; moreover, the studies have been rigorously controlled so that the efficacy of this drug is clearly established. Sumatriptan succinate reduces the intensity of acute headache attacks from "moderate to severe" to "mild or none" within two hours in 50% to 70% of patients following the oral administration of 100 mg and within an hour in 70% to 80% of patients following subcutaneous doses of 6 mg.[30] Headache recurs in 40% of patients within 24 hours, requiring another dose of the drug, probably because of its short half-life (2 hours).

Sumatriptan is effective for headache episodes that already peaked at the time of dosing, such as the early morning headache syndrome[32] and in menstrual-associated headaches,[33] the latter commonly waking women from sleep. Many patients say that they feel normal 15 minutes after taking a subcutaneous dose. No good data comparing sumatriptan with DHE are available; sumatriptan costs over four times more than DHE does.

The side-effect profile of sumatriptan is remarkably mild: warmth and tingling of the head and trunk are common and resolve shortly. Moreover, nearly 5% of patients report some chest discomfort that only rarely has been caused by myocardial ischemia. There is a consistent constrictor effect on the coronary artery circulation,[34] so that patients with coronary artery disease ought not receive this drug. For those at risk for coronary artery disease, such as older patients or those with diabetes mellitus or hypercholesterolemia, it has been suggested that the first dose of the drug be given with medical supervision.[35] It

also follows that sumatriptan and ergotamine should not be used concurrently.

Migraine Stabilization

A substantial number of drugs that have the capacity to stabilize the mechanism generating the symptoms that physicians recognize as migraine are now available. The probability of success with these drugs is greatly reduced in a patient with a drug-dependence cycle.[36] Such dependence can occur with ergotamine,[37] benzodiazepines,[36] corticosteroids,[39] all opiate analgesics, and aspirin and acetaminophen.[39] Any patient using analgesics daily without an interruption of 48 hours or more may be dependent and, therefore, not likely to benefit from antimigraine therapy until withdrawal is carried out. Intravenous DHE or phenothiazine therapy given in a hospital may be necessary for patients who sustain severe "rebound" headaches when they attempt withdrawal by simple abstinence.

If dependence is not a problem, the probability of success with any one of the antimigraine drugs is 60% to 70%, so that if one drug regimen is assessed each month, there may be an interval of several months before a patient's condition becomes stable. During this period it is usually necessary to provide the patient with an effective method for dealing with headache attacks that will not cause dependence; DHE and naproxen are highly suited for this purpose. Most patients are successfully managed with sequential monthly use of ergonovine maleate, propranolol hydrochloride or nadolol, and amitriptyline hydrochloride or nortriptyline hydrochloride (Table 1). If the situation demands urgent resolution, treatment with methysergide maleate or phenelzine sulfate can be implemented. The calcium channel antagonists have been disappointing.[40,41] Based on reports[42,43] and personal experience, valproate sodium appears to be remarkably effective.

Once effective stabilization is achieved, the drug therapy is continued for five to six months and then the dosage slowly tapered to assess its continued need. Many patients are able to discontinue medication and have fewer and less severe attacks for long periods of time,[44,45] suggesting that these drugs may alter the natural history of migraine.

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